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14. ABSTRACT

We conducted a feasibility study to assess the efficacy and safety of dietary soy for breast cancer prevention in pre-menopausal women at elevated risk of breast cancer. Mammographic breast density, a potential surrogate marker for breast cancer risk, was used as the primary entry criterion and the primary outcome. 47 pre-menopausal women with breast density ! 50% on mammography were randomized to either 25 mg/d of soy protein containing 50 mg total isoflavones or 25 mg/day of milk protein containing 0 mg of total isoflavones for 6 months. At randomization, the average 5-year Gail risk was 2.0% and the average breast density was 73% (range 59%-90%). The average change in percentage breast density was –2.7% in the soy arm and –2.4% in the placebo arm (p=0.48). There were no differences between groups in the change in IGF-1 or IGFBP3. The results of this study do not support the hypothesis that 6 months of soy protein reduces the risk of breast cancer in pre-menopausal women. However, the intervention was relatively short and the primary outcomes were surrogate markers of risk.

15. SUBJECT TERMS
soy isoflavones, breast cancer prevention, mammographic breast density, quality of life

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Introduction

The PREVENT study tested the feasibility and preliminary efficacy of soy supplementation to decrease risk of breast cancer in women with >50% breast density on mammography who are at elevated risk for breast cancer using the Gail model. Tamoxifen, the only prophylactic agent known to be effective for breast cancer, was initially used as a positive control to validate the use of the proposed surrogate markers including change in breast density. The randomized placebo controlled design allowed for comparative toxicity and efficacy determinations using patient symptom scores, validated quality of life tools, and adverse event profiles. Feasibility aims included assessment of the number of women randomized per month, dropout rates, and compliance with the study protein. Biological endpoints including changes in mammographic breast density and blood serum biomarkers (IGF-1/IGF-BP 3, hormone levels).

Body

Consumption of soy has increased dramatically in the United States over the past decade[1] based on a belief in soy's health benefits supported by industry marketing. However, the effects of soy consumption on breast cancer risk remains controversial.[2] Two meta-analyses of observational studies support the hypothesis that greater soy consumption is associated with lower risk for breast cancer.[3, 4] Animal model data is conflicting with some studies suggesting a protective effect of soy[5-7] and other studies suggesting an increased risk for breast cancer.[8-10]We conducted a feasibility study to assess the efficacy and safety of dietary soy for breast cancer prevention in premenopausal women at elevated risk of breast cancer. Mammographic breast density, a potential surrogate marker for breast cancer risk, was used as the primary entry criterion and the primary outcome.

The PREVENT trial is a randomized, placebo controlled study of 47 pre-menopausal women with breast density ≥ 50% on mammography. Women were randomized to either 25 mg/d of soy protein containing 50 mg total isoflavones or 25 mg/day of milk protein containing 0 mg of total isoflavones for 6 months. We assessed the feasibility of performing larger clinical trials of soy in women with elevated breast density by evaluating patient enrollment, compliance, and drop-out rates. The primary outcome measure of the study was the change in percent breast density on mammography timed to the menstrual cycle (days 7-13). Each woman had two standard mammographic views per breast obtained using an accredited dedicated mammography unit. The craniocaudal view was used to analyze breast density because it excludes the pectoralis muscle, which has been shown to create artifact when measuring breast density.[11] We measured breast density using the computer-based threshold method; software (Madena) for measuring density was obtained from Drs. Ursin and Astrahan.[12] For each mammographic image, a trained reviewer selected the best threshold to represent mammographic densities. The software counts both the total number of pixels and number of pixels within the defined dense breast area. The percentage of breast with densities is the ratio of the dense area to the total breast area. Novel measures of breast density including volumetric density and parenchymal complexity were also assessed. Additional outcome measures included analyses of serum IGF-1 and IGFBP-3 in blood drawn on the same day as the mammograms.

Primary Aim 1

Initial recruitment for the study was hampered by the inclusion of a tamoxifien arm as a positive control. Otherwise healthy women in the San Francisco Bay Area were unwilling to be randomized in a study that included the possibility of being randomized to tamoxifen. After

eliminating the tamoxifen arm, we randomized 47 women (see Figure 1), but never achieved a recruitment rate of more than 10 patients per month. Follow-up was complete for 40 women (85%) at the 6 month close out. The 15% dropout rate was better than the goal for the study (20%), but is still relatively high for a 6 month study. Among the 7 women who dropped out after randomization, 2 found the protein powder intolerable and one was concerned about weight gain. The other commonly reported reason for dropping out of the study was that the participant was too busy to continue. Compliance by packet count was good (88% among women completing the 6 month visit). The only side effects reported by more than one woman were stomach upset (18%), constipation (15%), heartburn (8%), hot flashes (5%), and diarrhea (5%). Most side effects were more common in the placebo arm (Table 1). There were no serious adverse events.

Figure 1: Flow of study participants

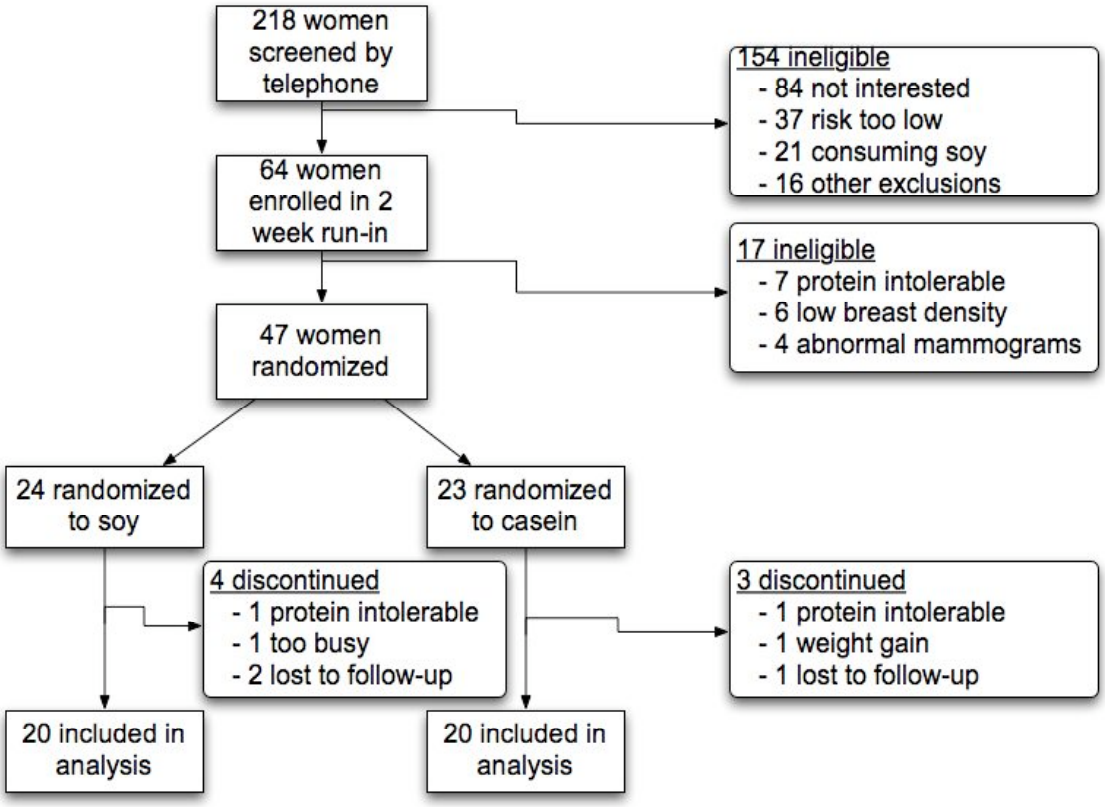


Table 1: Adverse events occurring in more than one participant

	Placebo	**Soy**
Upset stomach, %	20	15
Constipation, %	15	15
Heart burn, %	5	10
Hot flashes, %	10	0
Diarrhea, %	5	5

p>.50 for all comparisons

Baseline characteristics of the women are summarized in Table 2. At randomization, the average 5-year Gail risk was 2.0% and the average breast density was 74% (range 59%-90%). There were no statistically significant differences between the two groups.

Table 2: Baseline characteristics of participants completing the trial (n=40)

	Placebo	**Soy**
Age, years	44.6	44.8
Race, %		
White	70	80
Black	5	0
Asian	25	20
Family history of breast cancer, %	50	50
Breast density, %	72.3	73.3
5-year Gail risk, %	2.0	1.9
Age at menarche, years	13.1	12.9

Specific Aim 2

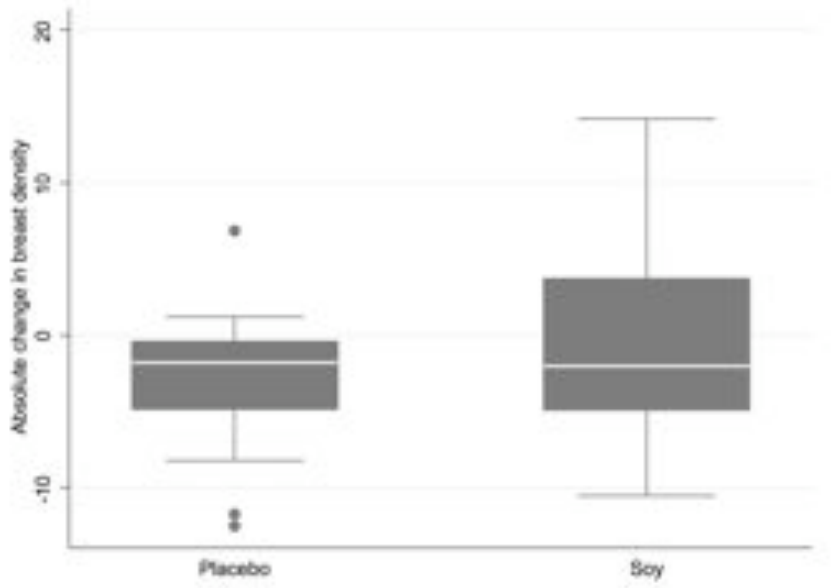
The primary outcome of the study was change in breast density from baseline after 6 months of soy protein containing 50 mg of isoflavones. Breast density was calculated as the ratio of dense areas on the cranial-caudal view of the mammogram to the total breast area measured on the same view. Overall breast density decreased from 72.8% to 70.9% over the 6 months of the study (p=0.03). However, there were no significant between group changes (Table 3). The box and whisker plot (Figure 2) demonstrates that women randomized to the soy arm had a much greater variability in the change in breast density compared to the placebo arm. The

distribution of the change scores was slightly skewed, but non-parametric analyses did not change the principal findings of the study (placebo median change -1.8%, soy median change -2.0%, p=0.48). Changes in novel measures of breast density using a phantom in the mammography field (single x-ray absorptiometry) or fractal geometry (parenchymal complexity), which attempt to improve the precision of breast density measurement by automatically calculating density without human input, did not differ between the soy and placebo arms.

Table 3: Mean change in breast density at 6 months

	Placebo	**Soy**	**p**
Measure			
Dense area	+0.2%	-0.4%	0.32
Total area	+12.8%	+3.2%	0.13
Percent density	-2.8%	-1.0%	0.30

Figure 2: Change in percentage breast density at 6 months



Specific Aim 3

We also measured the effect of soy protein on insulin-like growth factor 1 and it's principal binding protein, IGF-BP3, because they have been associated with premenopausal breast cancer[13-23] and with breast density in premenopausal women.[24-30] Neither the 6-month changes in measures of IGF-1 or IGF-BP3 nor changes in their ratio differed between the placebo and soy arms of the study (Table 4). Additional assays were not performed due to budgetary constraints.

Table 4: Change in IGF-1 and IGF-1 binding protein 3

	Placebo	Soy	p
IGF-1 (ng/ml)	-6.9	-13.3	0.66
IGF-BP3 (ng/ml)	-111	-57	0.85
IGF-1/IGF BP3	.0013	-.0035	0.36

Accomplishments, Challenges and Future Goals

Forms for collecting data related to all aspects of the study were designed, tested, and printed (Appendix A, first annual report). A computerized system with optical character recognition was been set up to facilitate data entry and validation. A software data verification system with extensive edits for range checks, missing data, and logical inconsistencies was designed and tested. Standard operating procedures were established for the involvement of numerous working groups at UCSF such as the Breast Care Center (BCC), mammography, radiology, phlebotomy and research lab staff. The final approval was obtained from the local Clinical Human Research committee (CHR) for the study protocol, informed consent, study brochure, as well as several informational tools (Appendix B, first annual report) that were provided to participants during the intervention period.

The start of the study was delayed due to complications relating to contract negotiations and agreement on details of the study protocol between the multiple agencies involved in the management and support of the project. The establishment of a contract with AstraZeneca, the manufacturer of tamoxifen, was delayed, but mutually agreeable terms were reached and both tamoxifen and identical placebo were received and packaged by our research pharmacy. The approval of the study protocol by the DOD required months of correspondence before a version that met the local IRB requirements, as well as the DOD, was achieved. The wording of the *Treatment and Compensation* clause in the informed consent which the local IRB requires specific wording was not acceptable to the DOD and resulted in an additional delay of a final approval several months.

Screening of women through the UCSF BCC Prevention program revealed that the original inclusion/exclusion criteria were too restrictive. In order to overcome this challenge we expanded the inclusion criteria to women with a family history of breast cancer that includes second-degree relatives, rather than the current model that only includes first-degree relatives.

Recruitment was a big challenge. During the first 2 months of recruitment, initial screening interviews were conducted with 41 women and of those more than half were found to not meet the study inclusion criteria. Of the 17 women who were found to be eligible, 14 stated they were not willing to join the study for various reasons. The majority of the eligible women who refused participation stated specifically that they did not want to risk random assignment to tamoxifen. Overall, the refusal rate of eligible women was approximately 90%. After careful review, it was decided that the refusal rate for the current study was unacceptable.

The study protocol was revised a second time, primarily dropping the tamoxifen arm of the study. Approval of the modified protocol was received in April 2003. The refusal rate for the study dramatically decreased after the introduction of the revised protocol and as of September 2003 it was at 30%. However, recruitment remained challenging. In response, a new recruitment strategy was developed to increase accrual.

The San Francisco Mammography Registry (SFMR) is a database containing information on persons receiving mammograms at a variety of public and private health care institutions in San Francisco. In cooperation with the SFMR we developed a direct mailing, inviting women who met eligibility criteria to participate in screening for our study. Use of the SFMR database allowed us to recruit women from a wide range of ethnicities and socioeconomic backgrounds as the registry includes women seen at clinics primarily serving patients on Medicaid and the uninsured. We obtained separate IRB approvals from all institutions participating in the collection of data for the SFMR before accessing the database and mailing letters to women. We mailed letters containing stamped refusal postcards to women in the SFMR who met our eligibility criteria and had expressly provided consent to be contacted about other studies on their SFMR questionnaire. Our first direct mailing took place in June 2004, with a second wave of letters mailed in August 2004. As a result of the modified protocol and targeted recruitment methods, accrual of study participants improved significantly.

In February 2005 we sent out a direct mailing to 409 women meeting basic eligibility criteria from the SFMR database. A response post card was received from 26% of the 409 women, with an initial refusal rate of 34% from the responders. After phone contact with the women responding with interest to learn more about study participation, 27 women were scheduled for a screening clinic visit, 22 declined a clinic visit and 21 were found to be ineligible after the phone screen.

Recruitment efforts were halted in July 2004 in order to have all eligible women screened and enrolled by a date that allowed for completion of the study protocol by the end of the calendar year. The best efforts were made to maximize the number of women screened each week in the final months of accrual, with an average of 3 women consented a week for 3 consecutive months. Due to the study requirement to time visits to a specific part of the menstrual cycle and the somewhat unpredictability of these cycles, it was a significant challenge to schedule all interested women by the end of July. One participant who is an excellent study candidate due to her extremely dense breast tissue was unable to start the study protocol until the middle of

August due to deviations in her menstrual cycle. Thus, the final patient close-out visit took place in February 2005.

Another challenge was the unscheduled contacts with participants in order to maintain their motivation to use the daily study protein. The ability of our study coordinator to keep motivation high in many women with differing personalities resulted in a mean adherence level above 80%.

Unfortunately, the study coordinator left for an industry position prior to finalization of the study database and completion of the study final report. This final challenge delayed the data lock and final analyses.

A manuscript presenting the study results is in preparation to be submitted by the end of the year. Ongoing collaborations with Dr. Maskarinec in Hawaii will continue to investigate the role of soy in breast cancer.

Key Research Accomplishments

- UCSF IRB approval of protocol 11/28/2001
- Development of new software for determining breast density
- Training of a radiologist in use of new procedure for determining breast density
- Validation of breast density analysis procedure using 144 sample images with percentage breast density ranging from 0% to 100%.
- Optimization of breast density analysis procedure for use with a G.E. digital mammography instrument, which will be used for all study mammograms
- Designed, tested and printed forms for data collection related to all aspects of the study (Appendix A in first annual report)
- Establishment of a computerized optical character recognition system for data entry and validation
- Development of standard procedures for the collection of biological specimens, including blood, urine and breast duct fluid
- Development of standard procedures for the transport, labeling and storage of biological specimens
- Establishment of contacts with practitioners outside of the UCSF group for referrals of eligible patients
- Development of informational tools to assist participants in following the approved protocol (Appendix B in first annual report)
- Development of procedures for the storage and dispensation of the study drugs with the research pharmacist, Monica Lee, PharmD.
- Soy protein powder and identical placebo received for Protein Technologies International, packaged and labeled by UCSF Cancer Center research pharmacy
- Tamoxifen and identical placebo received from AstraZeneca, packaged and labeled by UCSF Cancer Center research pharmacy
- Development and implementation of a direct mailing for recruitment of women from the San Francisco Mammography Registry
- Implementation of a direct mailing for recruitment of women from the San Francisco Mammography Registry
- 64 clinic Screening visits completed
- 47 randomization visits completed
- 40 3-month follow-up visits completed
- 40 close out (6-month) visit completed, last visit January 31, 2005.
- Data collected, reviewed for errors and entered into study database

- Data editing procedures completed for all data in the study database
- Biological samples (blood, urine, nipple aspirate and ductal lavage fluid) collected, processed and stored for analysis
- Digitization of mammography films and preparation of images for final analysis
- Primary analyses completed and presented at Era of Hope meeting in Philadelphia and at workshop on Soy and Breast Cancer in Chicago

Reportable Outcomes

1. Abstract P47; Era of Hope 2002.
2. Abstract p61-13; Era of Hope 2005.
3. Oral presentation at workshop: “Soy and Breast Cancer: Resolving the Controversy” Chicago, November 3, 2005.
4. Serving on DSMB for NCI supported BEAN 2 trial, a randomized clinical trial of the biological effects of soy on breast cancer markers.

Conclusions

We overcame significant challenges in patient recruitment and successfully completed 40 study closeout visits. We were unable to meet our accrual goal of 100 participants due to the many challenges faced early in the funding period but we are confident in the quality of our data. Recruitment for a prevention study that included a tamoxifen arm was difficult but targeting recruitment efforts to women with a history of dense mammograms was successful. Future studies focusing on women with elevated breast density are feasible, though large studies will require multiple sites for timely accrual of participants. Recruitment at mammography sites based on breast density may be a novel strategy useful in future studies of breast cancer etiology and prevention. We achieved good compliance with the soy protein, but patient retention was an issue. Ideally, we would like to achieve greater than 90% complete follow-up in this relatively short follow-up period. Future studies may benefit from the inclusion of a wider variety of soy foods in the intervention. The two week run-in period was useful for identifying women who were unable to comply with the dietary changes necessary to incorporate the protein powder into their daily meal patterns. Scheduling appointments based on the timing of a woman's menstrual cycle was particularly burdensome for the busy women enrolled in our study.

The study results suggest that 6-months of soy protein containing 50 mg of isoflavones does not significantly influence breast density, IGF-1, or IGF-BP3 in premenopausal women. Similar results have been reported by other investigators since the initiation of this study for both breast density[31-34] and both IGDF-1 and IGF-BP3.[35-43] Either these measurements are not good surrogate markers for breast cancer risk or soy isoflavones given during the late premenopausal phase of a woman's reproductive cycle do not influence her future risk of breast cancer.

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